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(54) Title: INHIBITORS OF ROTAMASE ENZYME ACTIVITY

(57) Abstract

This invention relates to the method of using neurotrophic pipecolic acid derivative compounds having an affinity for FKBP-type immunophilins as inhibitors of the enzyme activity associated with immunophilin proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity to stimulate or promote neuronal growth or regeneration.

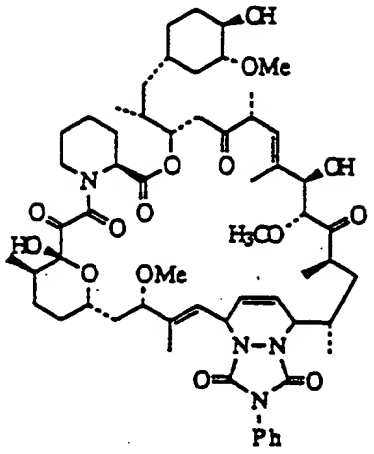
exist in a complex with FKBP-12. Dissociation of FKBP-12 from these complexes causes the calcium channel to become "leaky" (Cameron et. al., 1995) Calcium fluxes are involved in neurite extension so that the IP-3 receptor and the ryanodine receptor might be involved in the neurotrophic effects of drugs. Since the drugs bind to the same site on FKBP-12 as the IP-3 receptor or the ryanodine receptor, one would have to postulate that the drugs displace the channels from FKBP-12. No interaction between these calcium channels in cyclophilin has been reported so that this model would not explain the neurotrophic actions of cyclosporin A.

The neurotrophic actions of the drugs studied here are exerted at extremely low concentrations indicating potencies comparable to those of neurotrophic proteins such as brain derived growth factor, neurotropin-3 and neurotrophic growth factor.

The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All polymer molecular weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.

Illustrative pipecolic acid derivative compounds which can be used for the purposes of this invention include:

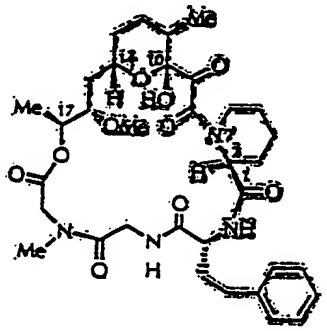
EXAMPLE 1



Way-124,466

This exemplary pipecolic acid derivative compound is disclosed by Ocain et al., *Biochemical and Biophysical Research Communications*, Vol. 192, No. 3, 1993. The compound was synthesized at Wyeth-Ayerst by Dr. Phil Hughes by reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with rapamycin.

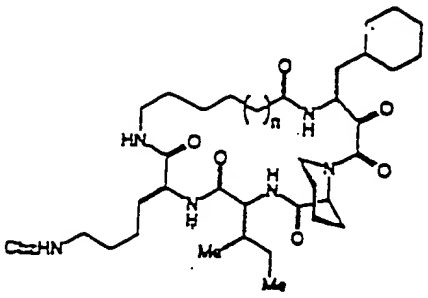
EXAMPLE 2



RAP-Pa

This pipecolic acid derivative compound is disclosed by Chakraborty et al., *Chemistry and Biology*, March 1995, 2:157-161.

EXAMPLES 3-5



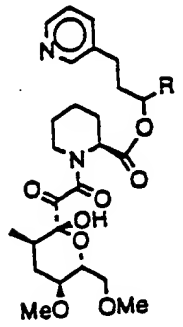
n
1
2
3

Exemplary pipecolic acid derivative compounds are disclosed by Ikeda et al., *J. Am. Chem. Soc.* 1994, 116, 4143-4144, and are incorporated herein by reference.

EXAMPLES 6-9

Exemplary pipecolic acid derivative compounds are disclosed by Wang et al., *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, No. 9, pp. 1161-1166, 1994, particularly compounds 2a-2d and are incorporated herein by reference.

EXAMPLE 10



This exemplary pipecolic acid derivative, compound 10, is disclosed by Birkenshaw et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 21, pp. 2501-2506, 1994, and is incorporated herein by reference.

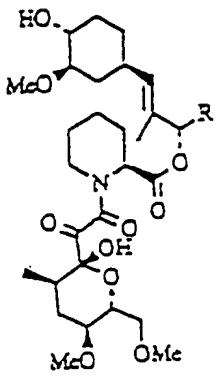
EXAMPLES 11-21

Exemplary pipecolic acid derivative compounds are disclosed by Holt et al., *J. Am. Chem. Soc.*, 1993, 115, 9925-9938, particularly compounds 4-14, and are incorporated herein by reference.

EXAMPLES 22-30

Exemplary pipecolic acid derivative compounds are disclosed by Caffery et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 21, pp. 2507-2510, 1994, and are incorporated herein by reference.

EXAMPLE 31



This exemplary pipecolic acid derivative, compound 31, is disclosed by Teague et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 3, No. 10, pp. 1947-1950, 1993 and is incorporated herein by reference.

EXAMPLES 32-34

Exemplary pipecolic acid derivative compounds are disclosed by Yamashita et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4., No. 2, pp. 325-328, 1994, particularly, compounds 11, 12, and 19, and are incorporated herein by reference.

EXAMPLE 35-55

Exemplary pipecolic acid derivatives are disclosed by Holt et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 2, pp. 315-320, 1994, particularly, compounds 3-21, and 23-24, and are incorporated herein by reference.

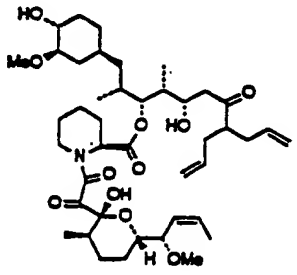
EXAMPLES 56-68

Exemplary pipecolic acid derivative compounds are disclosed by Holt et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 3, No. 10, pp. 1977-1980, 1993, particularly compounds 3-15 and are incorporated by reference herein.

EXAMPLES 69-83

Exemplary compounds of the present invention are disclosed by Hauske et al., *J. Med. Chem.* 1992, 35, 4284-4296, particularly compounds 6, 9-10, 21-24, 26, 28, 31-32, and 52-55, and are incorporated herein by reference.

EXAMPLE 84



SLB506

This exemplary pipecolic acid derivative is disclosed by Teague et al., *Bioorganic & Med. Chem. Letters*, Vol. 4, No. 13, pp. 1581-1584, 1994, and is incorporated herein by reference.

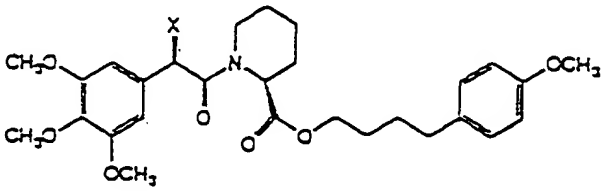
EXAMPLES 85-88

Exemplary pipecolic acid derivative compounds are disclosed by Stocks et al., *Bioorganic & Med. Chem. Letters*, Vol. 4, No. 12, pp. 1457-1460, 1994, particularly compounds 2, 15-17 and are incorporated herein by reference.

EXAMPLES 90-111

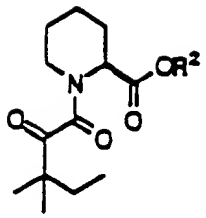
Additional exemplary pipecolic acid derivatives are described in Scheme 10, Tables 1-5.

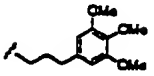
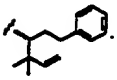
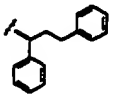
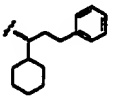
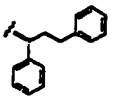
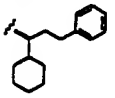
SCHEME 01



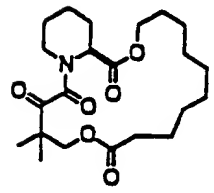
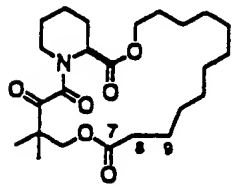
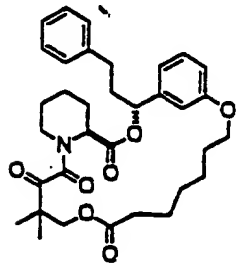
EXAMPLE/COMPOUND	STRUCTURE
6	X = H_2
7	X = CH_2
8	X = H, CH_3
9	X = O

SCHEME 2



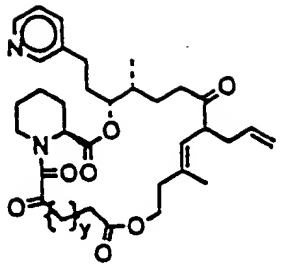
EXAMPLE/COMPOUNDS No.	R_2
11	
12	
13	
14	
15	
16	
17	
18	

SCHEME 3

EXAMPLE/COMPOUND NO.	STRUCTURE
19	
20	
21	

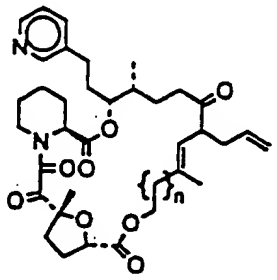
Scheme 4

Table 1



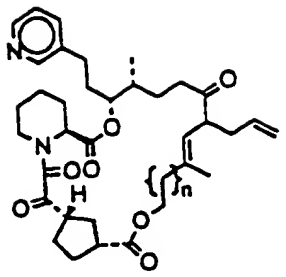
Example/Compound No.	Structure
24	y=1
23	y=2
24	y=3

Table 2



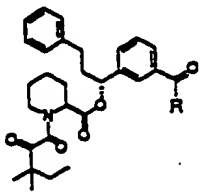
Example/Compound No.	Structure
25	n=1
26	n=2
27	n=3

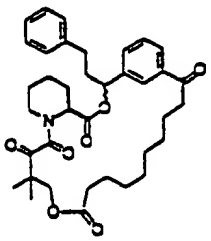
Table 3.



Example/Compound No.	Structure
28	n=1
29	n=2
30	n=3

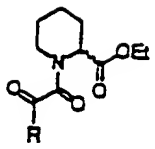
SCHEME 5



EXAMPLE/COMPOUND No.	STRUCTURE
32	R=phenyl
33	R=N(allyl)$_2$
34	

Scheme 6

Table 1



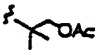
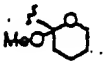
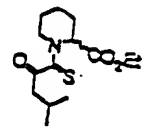
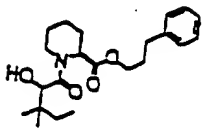
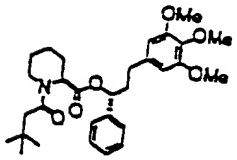
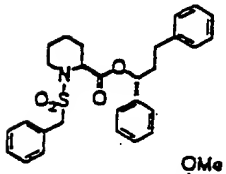
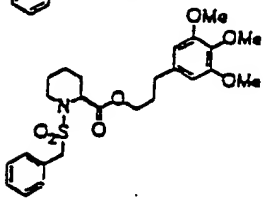
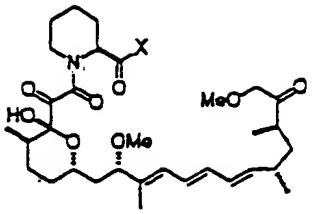
Example/Compound No.	Structure R
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	

Table 2

Example/Compound No.	Structure
51	
52	
53	
54	
55	

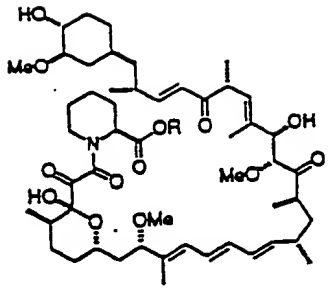
SCHEME 7

TABLE 1



56	x = OH
57	x = OMe
58	x = Oi Pr
59	x = OBn
60	x = OCH MePh
61	x = $OCH_2CHCHPh$
62	x = $OCH_2CH_2CH_2(3,4\text{-}OMe_2)Ph$
63	x = NHBn
64	x = $NHCH_2CH_2CH_2Ph$

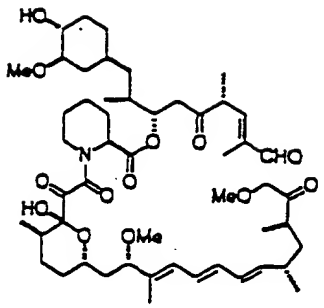
Table 2



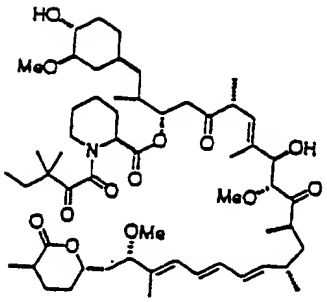
65	R = Me
66	R = Bn

Table 3

67

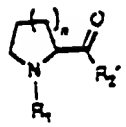


68



Scheme 8

Table 1



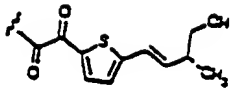
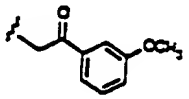
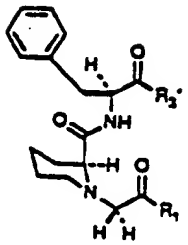
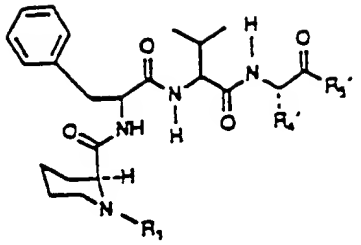
Example/Compound No.	Structure
69	n = 2, R_1 =  R_2 = Phe-o-tert-butyl
70	n = 2, R_1 =  R_2 = Phe-o-tert-butyl

Table 2



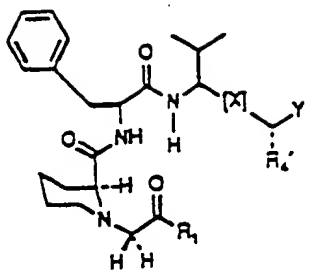
71	R_1=m-OCH_3Ph; R_3^1=Val-o-tert-butyl
72	R_1=m-OCH_3Ph; R_3^1=Leu-o-tert-butyl
73	R_1=m-OCH_3Ph; R_3^1=Ileu-o-tert-butyl
74	R_1=m-OCH_3Ph; R_3^1=hexahydro-Phe-o-tert-butyl
75	R_1=m-OCH_3Ph; R_3^1=allylalanine-o-tert-butyl
76	R_1=B-naphthyl; R_3^1=Val-o-tert-butyl

Table 3



Example/Compound No.	Structure
77	R_1 = $CH_2(CO)$-m-OCH_3PH R_4^1 = CH_2Ph R_5^1 = OCH_3
78	R_1 = $CH_2(CO)$-B-naphthyl R_4^1 = CH_2Ph R_5^1 = OCH_3

Table 4



Example/Compound No.	Structure
79	R_1 = m-OCH_3Ph X = trans-CH=CH R_4^1 = H Y = OC(o)Ph
80	R_1 = m-OCH_3Ph X = trans-CH=CH R_4^1 = H Y = $OC(o)CF_3$
81	R_1 = m-OCH_3Ph X = trans-CH=CHI R_4^1 = - Y = -
82	R_1 = m-OCH_3Ph X = trans-CH=CH R_4^1 = H Y = $OCH_2CH=CH_2$
83	R_1 = m-OCH_3Ph X = C=O R_4^1 = H Y = Ph

Scheme 9

Table 1

85

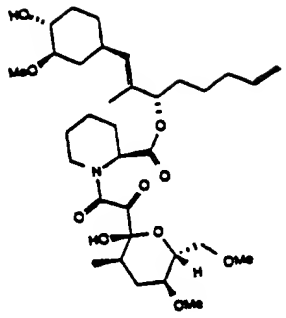
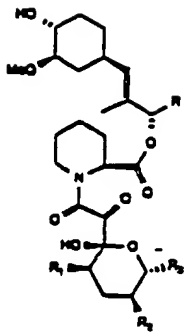


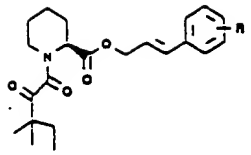
Table 2



86	R_1=H,	R_2=OMeR_3=CH_2OMe
87	R_1=H,	R_2=R_3=H
88	R_1=Me,	R_2=R_3=H

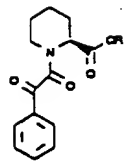
Scheme 10

Table 1



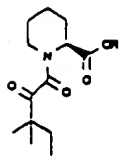
Example	R =
90	3,4-dichloro
91	3,4,5-trimethoxy
92	H
93	3-(2,5-Dimethoxy)-phenylpropyl
94	3-(3,4-Methylene-dioxy)phenylpropyl

Table 2



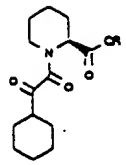
Example	R =
95	4-(*p*-Methoxy)-butyl
96	3-Phenylpropyl
97	3-(3-Pyridyl)-propyl

Table 3



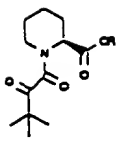
Example	R =
98	3-(3-Pyridyl)-propyl
99	1,7-Diphenyl-4-heptyl
100	4-(4-Methoxy)butyl
101	1-Phenyl-6-(4-methoxy-phenyl)-4-hexyl
102	3-(2,5-Dimethoxy)phenyl-propyl
103	3-(3,4-Methylenedioxy)-phenylpropyl
104	1,5-Diphenylpentyl

Table 4



Example	R =
105	4-(4-Methoxy)butyl
106	3-Cyclohexylpropyl
107	3-Phenylpropyl

Table 5



Example	R =
108	3-Cyclohexylpropyl
109	3-Phenylpropyl
110	4-(4-Methoxy)butyl
111	1,7-Diphenyl-4-heptyl

NEUROTROPHIC EFFECTS OF ROTAMASE INHIBITORS

Table I lists a number of the claimed examples together with their potencies to induce trophic effects in cultured sensory neurons, as described above. Figures 19 and 20 show photomicrographs of Example 111 and Example 17 promoting neurite outgrowth in the dorsal root ganglion cultures.

Table I
In Vitro Potencies of Test Examples

Example	Rotamase Inhibition K_i, nM	Neutrophic ED_{50} Chick DRGs, nM
6	140	25
9	13	0.030
11	170	1
12	250	300
13	25	80
15	17	0.30
19	12	0.017
36	>10,000	>10,000
41	1300	5000
50	>10,000	>10,000
90	1800	2500
91	28	200
92	39	90
93	75	35
94	70	8
95	165	5-10
96	740	10-20
97	725	150
98	130	75
99	30	5
100	60	43
101	15	0.17
102	12	2.5
103	120	3
104	20	.016
105	103	6
106	760	1
107	210	0.82
108	32	0.29
109	2	0.08
110	24	0.002
111	5	0.08